

REMARKS

Prior to entry of the Amendment, Claims 15 - 32 and 34 - 40 were pending in the application. With this Amendment Claims, Claims 15, 17, 25 and 31 have been amended to clarify what Applicants consider the subject matter of the invention. Support for the amendment to Claim 15, 17, 25 and 31 is found in the specification as originally filled, including paragraphs [0021] and [0036], for example. No new matter is introduced by these amendments. In addition, with this Amendment, Claims 34, 35, 39, 40 are canceled without prejudice. With this amendment, Claims 41 – 54 are newly added. Support for new claims 41 – 54 is found in the specification as originally filled, including the originally filed claims, paragraphs [0017], [0021] [0023], [0025]and [0036], for example. No new matter is introduced by these claims.

Applicants retain the right to file further continuation and divisional applications on any non-elected claim and on the subject matter of any claim previously or presently canceled.

Drawings

Applicants acknowledge that the objection to the drawings has been withdrawn.

Notice of References Cited

Applicants acknowledge the receipt of the Notice of References Cited (PTO-982) with the Office Action of December 27, 2007. Applicants would like to bring to the Patent Offices' attention that the Notice of References Cited (PTO-982) was blank and requests that the Patent Office provide Applicants with a copy of a completed and initialed Notice of References Cited (PTO-982).

Claim Rejections under 35 USC §102(b) and (e) Withdrawn

Applicants acknowledge that the rejection of Claims 15 – 28, 31 – 32 and 34 – 40 in light of *Mitchinson* (U.S. Patent 6,268,328) and *Fowler* (U.S. Patent 6,407,046)

under 35 USC §102(b), have been withdrawn. Applicants acknowledge that the rejection of Claims 15 – 28, 23 – 29 and 34 – 40 in light of *Lehmbeck* (U.S. Patent 6,352,841) under 35 USC §102(e), has been withdrawn.

Claim Rejections under 35 USC §112, first paragraph

The Claims Meet the Written Description Requirement

Applicants acknowledge that the prior rejection of Claims 16 and 19 – 22, under 35 USC §112, written description have been withdrawn. In the present Office Action the Patent Office has rejected Claims 15, 17 – 18, 23 – 32 and 34 – 40 under 35 USC §112, first paragraph, as allegedly not meeting the written description requirement. Applicants respectfully disagree with the rejection.

The Patent Office correctly states that the specification properly describes the means of producing an inducing feed comprising sophorose and gentiobiose (Office Action, page 4). The Patent Office further states the specification does not provide adequate description of the means by which an inducing feed comprising other inducers is produced. Applicants respectfully disagree. Further the Patent Office states that the rejected claims encompass the production of a protein of interest utilizing any promoter not just those promoters that are sophorose- or gentiobiose-inducible (Office Action, page 4). Applicants respectfully disagree.

In order to satisfy the written description requirement of 35 U.S.C. § 112, the application must reasonably convey to one skilled in the art that the applicant was in possession of the claimed subject matter at the time the application was filed. *Vas-Cath v. Mahurkar*, 935 F.2d 1555, 1563, 19 USPQ2d (BNA) 1111, 1117 (Fed Cir. 1991). Every species encompassed by the claimed invention, however, need not be disclosed in the specification to satisfy the written description requirement of 35 U.S.C. § 112, first paragraph. *Utter v. Hiraga*, 845 F.2d 993, 6 USPQ2d 1709 (Fed. Cir. 1988). The Federal Circuit has made it clear that sufficient written description requires simply the knowledge and level of skill in the art to permit one of skill to immediately envision the product claimed from the disclosure. *Purdue Pharm L.P. v. Faulding Inc.*, 230 F.3d 1320,

1323, 596 USPQ2d 1481, 1483 (Fed. Cir. 2000) ("One skilled in the art must immediately discern the limitations at issue in the claims.").

Applicants respectfully submit that the written description requirement for rejected Claims 15, 17 – 18, 23 – 32 and 34 – 40 under 35 USC §112, first paragraph, is satisfied for reasons of record and the following statements. Applicant's patent specification describes the claimed invention in sufficient detail that one skilled in the art can reasonably conclude that the inventor had possession of the claimed invention. In particular, the specification defines an inducing feed as "a solution fed to a microorganisms that causes or induces the production of desired protein product" (specification, page 13). However, the Patent Office stated that this is insufficient to meet the written description requirement (Office Action, page 4). Applicants respectfully disagrees, and respectfully submit that in paragraph [0057] the specification recites: "Induction" refers to the increased transcription of a gene resulting in the synthesis of a protein of interest in a cell or organism at a markedly increased rate in response to the presence of an "inducer". To measure the induction of a protein of interest, cells treated with a potential inducer are compared to control samples without the inducer. Control samples (untreated with inducers) are assigned a relative protein activity value of 100%. Induction of a polypeptide is achieved when the activity value relative to the control (untreated with inducers) is greater than 100%, greater than 10%, more preferably 150%, more preferably 200-500% (i.e., two to five fold higher relative to the control), or more preferably 1000-3000% higher. Accordingly, the specification reasonably conveys to one skilled in the art that the applicant was in possession of the claimed subject matter at the time the application was filed. The specification clearly provides adequate description of the means by which an inducing feed comprising inducers are produced, and how to assay for induction.

As set forth above, the specification describes the claimed invention in sufficient detail that one skilled in the art can reasonably conclude that the inventor had possession of the claimed invention and the rejection of the claims under 35 U.S.C. § 112, first paragraph for lack of written description should be withdrawn.

While Applicants maintain that the claims as originally filed and previously amended were sufficiently supported by the specification, the claims have been amended to further prosecution. Solely to expedite prosecution and without

acquiescence to the rejection, independent Claim 15 has been amended to specify that the inducing feed composition comprises sophorose and/or gentiobiose, and glucose; and to specify that the inducible promoter is a sophorose-inducible promoter or a gentiobiose-inducible promoter. In view of the foregoing, Applicants respectfully submit that the claims meet 35 U.S.C. §112, first paragraph.

Claim Rejections under 35 USC §103(a)

The Claims are Non-Obvious over *Mitchinson and Kamo*

The Patent Office has rejected Claims 15 - 32 and 34 - 40 under 35 USC §103(a), as allegedly being unpatentable over by *Mitchinson et al.* (US Pat. No. 6,268,328), herein after “*Mitchinson*” in light of *Kamo et al.* (JP patent 05211883) herein after “*Kamo*”. Applicants respectfully traverse the rejection.

The Patent Office asserts that the instant claims are drawn to methods of producing an inducing feed ... (Office Action, page 7). Applicants respectfully submit that the instant claims are directed to a method for producing a protein, rather than a method of producing an inducing feed composition.

In the present Office Action the Patent Office asserts that *Mitchinson* discloses methods of recombinantly producing cellulases utilizing host cells comprising expression vectors wherein said host cells can be either bacterial, yeast, or fungal. *Mitchinson* further disclose that the bacterial host cells can be either *Bacillus subtilis* and the fungal host cells can be *Trichoderma reesei*. Moreover, *Mitchinson* disclose that the expression vector further comprises an inducible promoter and that said promoter can be *cbh1*. Additionally, *Mitchinson* disclose that the expressed protein can be heterologous to the host cells. While *Mitchinson* do not explicitly disclose that the promoters used are sophorose or gentiobiose inducible, the disclosed *cbh1* promoter possesses these characteristics the Patent Office asserts (Office Action, page 8).

The Patent Office correctly asserts that *Mitchinson* fails to disclose methods for making an inducing feed from a composition comprising a high glucose solution. The Patent Office further states that *Kamo* discloses methods of making sophorose and gentiobiose from a composition comprising 10 – 90% glucose (Office Action, page 8).

Applicants assert that *Mitchinson* and *Kamo*, alone or in combination fails teach or suggest all the elements of claims 15 - 32 and 34 - 40. For example, independent Claim 15 is directed to a method for producing a protein of interest and specifically recites the steps of:

- a) Mixing a concentrated glucose solution comprising between about 5% to about 75% glucose with a cellulase preparation selected from the group consisting of a whole cellulase composition or beta-glucosidase enriched cellulase composition to give a first mixture;
- b) Incubating the first mixture at a temperature and for a sufficient time to produce an inducing feed composition; and
- c) Culturing a host cell with said inducing feed composition in an amount effective to induce the production of said protein of interest.

Applicants assert that *Mitchinson* and *Kamo*, alone or in combination fails teach or suggest all the elements of independent Claims 15 and the claims dependent thereon. While *Mitchinson* states that “Any growth medium can be used in the present invention that is suitable to grow the desired transformants” and refers to a “liquid media” it lacks the steps required of independent Claim 15 (a) - (c), and the claims dependent thereon, and likewise *Kamo* fails teach or disclose each these steps.

Kamo is directed to methods of manufacturing sophorose from glucose (*Kamo* at [0001] and [0008]). In contrast, the rejected claims require culturing a host cell with the inducing feed composition. As described in Applicants specification the final solution is used for fermentation feeding, while *Kamo* describes removal of unreacted glucose after the end of the reaction (*Kamo* at [00014]), and fails to teach or suggest culturing a cell with an inducing feed composition.

Applicants assert that *Mitchinson* and *Kamo*, either alone or in combination, fail teach or suggest every limitation of recited in independent Claim 15 and the claims dependent thereon. Accordingly, Applicants submit that Patent Office’s reliance on *Mitchinson* and *Kamo* fails to render the method of Claim 15 and the claims dependent thereon *prima facie* obvious. In view of the foregoing, Applicants respectfully request that the rejection of Claims 15 - 32 and 34 - 40 under 35 USC §103(a), as allegedly being unpatentable over by *Mitchinson* in light of *Kamo* be withdrawn.

The Claims are Non-Obvious over *Fowler and Kamo*

The Patent Office has rejected Claims 15 - 32 and 34 - 40 under 35 USC §103(a), as allegedly being unpatentable over *Fowler et al.* (US Pat. No. 6,407,046), herein after "*Fowler*" in light of *Kamo*. Applicants respectfully traverse the rejection.

In the present Office Action the Patent Office asserts that *Fowler* discloses methods of recombinantly producing cellulases utilizing host cells comprising expression vectors wherein said host cells can be either bacterial, yeast, or fungal. *Fowler* further discloses that the bacterial host cells can be either *Bacillus subtilis* and the fungal host cells can be *Trichoderma reesei*. Moreover, *Fowler* discloses that the expression vector further comprises an inducible promoter and that said promoter can be *cbh1*. Additionally, *Fowler* discloses that the expressed protein can be heterologous to the host cells. While *Fowler* do not explicitly disclose that the promoters used are sophorose or gentiobiose inducible, the disclosed *cbh1* promoter possesses these characteristics the Patent Office asserts (Office Action, page 9).

The Patent Office correctly asserts that *Fowler* fails to disclose methods for making an inducing feed from a composition comprising a high glucose solution. The Patent Office further states that *Kamo* discloses methods of making sophorose and gentiobiose from a composition comprising 10 – 90% glucose (Office Action, page 8).

Applicants assert that *Fowler* and *Kamo*, alone or in combination fail teach or suggest all the elements of claims 15 - 32 and 34 - 40. For example, independent Claim 15 is directed to a method for producing a protein of interest. Applicants assert that *Fowler* and *Kamo*, alone or in combination fail teach or suggest all the elements of independent Claims 15 and the claims dependent thereon. *Fowler* lacks the steps required of independent Claim 15 (a) - (c), and the claims dependent thereon, and likewise, *Kamo* fails teach or disclose each these steps.

As described above, *Kamo* is directed to methods of manufacturing sophorose from glucose (*Kamo* at [0001] and [0008]). In contrast, the rejected claims require culturing a host cell with the inducing feed composition. As described in Applicants' specification the final solution is used for fermentation feeding, while *Kamo* describes removal of unreacted glucose after the end of the reaction (*Kamo* at [00014]), and fails

to teach or suggest culturing a cell with an inducing feed composition.

Applicants assert that *Fowler* and *Kamo*, either alone or in combination, fail teach or suggest every limitation of recited in independent Claim 15 and the claims dependent thereon. Accordingly, Applicants submit that Patent Office's reliance on *Fowler* and *Kamo* fail to render the method of Claim 15 and the claims dependent thereon *prima facie* obvious. In view of the foregoing, Applicants respectfully request that the rejection of Claims 15 - 32 and 34 - 40 under 35 USC §103(a), as allegedly being unpatentable over by *Fowler* in light of *Kamo* be withdrawn.

The Claims are Non-Obvious over *Lehmbeck* and *Kamo*

The Patent Office has rejected Claims 15 - 32 and 34 - 40 under 35 USC §103(a), as allegedly being unpatentable over *Lehmbeck et al.* (US Pat. No. 6,352,841), herein after "*Lehmbeck*" in light of *Kamo*. Applicants respectfully traverse the rejection.

In the present Office Action the Patent Office asserts that *Lehmbeck* discloses methods of recombinantly producing cellulases utilizing host cells comprising expression vectors wherein said host cells can be either bacterial, yeast, or fungal. *Lehmbeck* further discloses that the bacterial host cells can be either *Bacillus subtilis* and the fungal host cells can be *Trichoderma reesei*. Moreover, *Lehmbeck* discloses that the expression vector further comprises an inducible promoter and that said promoter can be *cbh1*. Additionally, *Lehmbeck* discloses that the expressed protein can be heterologous to the host cells. While *Lehmbeck* does not explicitly disclose that the promoters used are sophorose or gentiobiose inducible, the disclosed *cbh1* promoter possesses these characteristics the Patent Office asserts (Office Action, page 10).

The Patent Office correctly asserts that *Lehmbeck* fails to disclose methods for making an inducing feed from a composition comprising a high glucose solution. The Patent Office further states that *Kamo* discloses methods of making sophorose and gentiobiose from a composition comprising 10 – 90% glucose (Office Action, page 8).

Applicants assert that *Lehmbeck* and *Kamo*, alone or in combination fail teach or suggest all the elements of claims 15 - 32 and 34 - 40. For example, independent Claim 15 is directed to a method for producing a protein of interest. Applicants assert that *Lehmbeck* and *Kamo*, alone or in combination fail teach or suggest all the elements of independent Claims 15 and the claims dependent thereon. *Lehmbeck* lacks the steps

required of independent Claim 15 (a) - (c), and the claims dependent thereon, and likewise, *Kamo* fails teach or disclose each these steps.

As described above, *Kamo* is directed to methods of manufacturing sophorose from glucose (*Kamo* at [0001] and [0008]). In contrast, the rejected claims require culturing a host cell with the inducing feed composition. As described in Applicants' specification the final solution is used for fermentation feeding, while *Kamo* describes removal of unreacted glucose after the end of the reaction (*Kamo* at [00014]), and fails to teach or suggest culturing a cell with an inducing feed composition.

Applicants assert that *Fowler* and *Kamo*, either alone or in combination, fail teach or suggest every limitation of recited in independent Claim 15 and the claims dependent thereon. Accordingly, Applicants submit that Patent Office's reliance on *Lehmbeck* and *Kamo* fail to render the method of Claim 15 and the claims dependent thereon *prima facie* obvious. In view of the foregoing, Applicants respectfully request that the rejection of Claims 15 - 32 and 34 - 40 under 35 USC §103(a), as allegedly being unpatentable over by *Lehmbeck* and *Kamo* be withdrawn.

The Claims are Non-Obvious over *Mitchinson*, *Fowler*, *Lehmbeck* and *Kamo*

Assuming *arguendo*, that the Patent Office has met the *prima facie* case for obviousness rejection, which Applicants maintain it has not with respect to *Mitchinson*, *Fowler*, *Lehmbeck* and *Kamo*, Applicants submit that the claims rejected claims are not obvious.

The Patent Office submits that it would have been obvious for the skilled artisan to incorporate the methods of *Kamo* with those of *Mitchinson*, *Fowler*, or *Lehmbeck* in order to take advantage of the inexpensive means of producing sophorose and gentiobiose and to take advantage of the increased production associated with the use of sophorose and gentiobiose-inducable promoters (Office Action at pages 8, 9 and 11). Applicants respectfully disagree.

Applicants submit that *Mitchinson* and *Kamo* , or *Fowler* and *Kamo*, or *Lehmbeck* and *Kamo* can not be combined because the references teach away from their combination. Applicants submit that it is improper to combine references where the

references teach away from their combination. In re Grasselli, 713 F.2d 731, 743, 218 USPQ 769, 779 (Fed. Cir. 1983)

As described in the specification, commercial scale production of cellulase enzymes is by either solid or submerged culture including batch, fed batch, and continuous flow processes. One of the most problematic and expensive aspect of industrial cellulase production is providing the appropriate inducer to *Trichoderma*. As is the case for laboratory scale experiments, cellulase production on a commercial scale is induced by growing the fungus on solid cellulose or by culturing the organism in the presence of a disaccharide inducer such as lactose. Unfortunately on an industrial scale, both methods of induction have drawbacks which result in high costs being associated with cellulase production (Specification at [010]).

Importantly, cellulase synthesis is subject glucose repression. Thus, a critical factor influencing the yield of cellulase enzymes or heterologous proteins under the control of an inducible promoter is the maintenance of a proper balance between cellulose substrate and glucose concentration; it is critical for obtaining reasonable commercial yields of the regulated gene product. Although cellulose is an effective and inexpensive inducer, controlling the glucose concentration when *Trichoderma* is grown on solid cellulose can be problematic. At low concentrations of cellulose, glucose production may be too slow to meet the metabolic needs of active cell growth and function. On the other hand, cellulase synthesis can be halted by glucose repression when glucose generation is faster than consumption. Thus, expensive process control schemes are required to provide slow substrate addition and monitoring of glucose concentration (Ju and Afolabi, Biotechnol. Prog., 91-97, 1999). Moreover, the slow continuous delivery of substrate can be difficult to achieve as a result of the solid nature of the cellulosic materials (Specification at [011]). Some of the problems associated with the use of cellulose as an inducing substrate can be overcome through the use of soluble substrates and inducers such as lactose or sophorose. Lactose has to be provided at high concentrations so as to function as an inducer and a carbon source. (See Seiboth, et. al., Mol. Genet. Genomics, 124-32, 2002.) Gentiobiose may also serve as an inducer. Sophorose is a more potent inducer than cellulose, but sophorose is expensive and difficult to manufacture. Thus, while it is easier to handle and control than solid cellulose, sophorose can nonetheless make the cost of producing cellulases

prohibitively expensive and, thus, is impractical for commercial cellulase production. Clearly, a need exists for a convenient, soluble substrate composition that also provides an inexpensive method of cellulase induction in filamentous fungi, *e.g.*, *Trichoderma reesei*.

Kamo is directed to methods of manufacturing sophorose from glucose (*Kamo*, at [0001] and [0008]) and the “results in which this invention persons examined wholeheartedly how to separate sophorose from the mixture ...” [0012] (emphasis added). In addition, *Kamo* describes removal of unreacted glucose after the end of the reaction “ [00014] (emphasis added). Applicants assert that the cited references teach away from the invention (see MPEP § 2141.02 prior art must be considered in its entirety, including disclosures that teach away from the claims). Applicants submit that the fact that the cited references teaches away from the claimed invention is a significant factor to be considered in determining obviousness.

In addition, Applicants assert that the claimed invention yields unexpectedly improved properties or properties not present in the prior art. Here the claimed methods for producing a protein rely in part on the complex mixture that is sufficient to induce cellulase production “as is” without further purification (Specification at [015]). As described the specification, this discovery is surprising since glucose acts as a repressor of cellulase genes in *Trichoderma reesei*. In addition, this discovery provides an inducer of cellulase gene expression that is an inexpensive alternative to lactose or purified sophorose and a less cumbersome alternative to solid cellulose for the production of proteins (Specification at [015] and [034]).

Applicants assert that *Mitchinson*, *Fowler*, *Lehmbeck* and *Kamo*, either alone or in combination, fail to render the claims obvious under 35 USC §103(a). In view of the foregoing, Applicants respectfully request that the rejection of claims under 35 USC §103(a), be withdrawn.

CONCLUSION

As all of the Examiner's rejections and arguments have been herein addressed and in light of the above remarks, the Applicants respectfully submit that the pending claims are in condition for allowance. Thus, Applicants respectfully request that a Notice of Allowance be issued at an early date. If a telephone conference would expedite prosecution of this application, the Examiner is invited to telephone the undersigned at (650) 846-7614.

Respectfully submitted,

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